Statistical analysis plan (SAP) and study protocol

Official title: Implementation and Evaluation of Prolonged Exposure Psychotherapy for Adverse Events in Early Phase Psychosis with Comorbid Substance Misuse

Brief title: Psychotherapy for psychosis, adverse events, and substance misuse

NCT#04546178

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Acronyms

AE(s)	Adverse event(s)
SM	Substance misuse
EPP	Early phase psychosis
PE	Prolonged Exposure therapy
PE+	Adapted Prolonged Exposure therapy
NSEPP	Nova Scotia Early Psychosis Program
MBD	Multiple baseline design
RCI	Reliable change index

Plain-language summary and rationale

Research has found that adversity (e.g., abuse) and substance misuse (i.e., problematic drug and alcohol use) can affect how much a person recovers from a psychotic disorder (e.g., schizophrenia, schizoaffective disorder). This can cause problems, given that people with psychotic disorders seem to experience more adverse events (i.e., difficult, or upsetting events that are out of their control) and are more likely to misuse drugs and/or alcohol to the point that they have a hard time doing important things like going to work or school. There are not a lot of treatment options for people living with a psychotic disorder, substance misuse, and adversity-related symptoms (e.g., anxiety, depression) – most treatment studies that target adversity-related sequelae (e.g., anxiety, PTSD) have excluded people with a psychotic disorder or drug/alcohol use from their therapy studies, so we know little about what treatments are effective for these individuals. We know even less about young adults who are in the first years of a psychotic illness (i.e., early phase psychosis; EPP). Compared to people with chronic psychosis (i.e., having a psychotic disorder for over 10 years), people in EPP may be more likely to recover once they get help for their mental health problems because they haven't been ill as long, and they haven't been using drugs or alcohol for as long. Other research has shown that Prolonged Exposure (PE), a type of cognitive-behavioural therapy (CBT), might be a good fit for people with EPP, but there isn't much information about how helpful this treatment is for people with psychotic disorders, or how to adapt this therapy for people in EPP. The goal of this study is to adapt PE therapy for young adults in EPP and measure its effect on adversity-related sequelae (e.g., anxiety), substance misuse, and psychotic symptoms. We plan to include 20 people in this study from the Nova Scotia Early Psychosis Program (NSEPP) who are 19-35 years old. These participants will each participate in 15 individual sessions of adapted PE (i.e., PE+); we will compare their questionnaire scores before, during, and after treatment to see if there are any changes to their psychotic symptoms (e.g., hallucinations), substance misuse, and adversity-related problems (e.g., depression). We aim to target two things that might be making things worse: avoidance and hopelessness. These two things can be targeted by asking people to face reminders of the negative or upsetting event(s) they experienced and by both finding new ways to think about the event and mental health challenges and learning new skills to cope with mental health symptoms.

Objectives & hypotheses

Study objectives

(O1): Establish the ideal treatment duration (i.e., number of sessions) that results in clinically significant change for participants
(O2): Establish the effect of PE+ therapy on the severity of psychotic symptoms, adversity-related symptoms (e.g., anxiety, insomnia), substance misuse, and overall functioning.

Hypotheses

(H1): PE+ treatment will result in clinically significant reductions in hopelessness and avoidance

(H2): PE+ treatment will result in clinically significant reductions in negative psychotic symptoms (e.g., anhedonia)
(H3): PE+ treatment will result in clinically significant reductions in the frequency and quantity of SM by 2-months post-treatment.
(H4): A global improvement in functioning from pre- to post-PE+ therapy will occur, with gains maintained 2 months-post treatment.

Methods

Research Plan

This study involves adapting and optimizing PE therapy for adults in early phase psychosis (i.e., PE+). Participants will be asked to tell us about themselves (e.g., race, gender), participate in interviews, and complete questionnaires assessing their current psychosis- and adversity-related symptoms (e.g., anxiety, depression) and substance misuse, along with avoidance and hopelessness. Participants will participate in 15 psychotherapy sessions targeting adversity-related sequelae. Symptom change will be evaluated throughout their participation and as an outcome.

A multiple-baseline design (MBD; Kratochwill et al., 2010) will be used to stringently examine intervention effects; this design temporally staggers intervention start times across participants, thereby creating a control group composed of each individual's pre-intervention scores. Randomization of start time will be used to increase internal validity and minimize bias (Kratochwill & Levin, 2010). The MBD allows a fine-grained assessment of each component of the intervention; this design can detect significant change during each phase of the intervention. An MBD is well-suited to a study focused on adaptation and optimization of a psychotherapy as it will provide insight on what components have more or less effectiveness in EPP.

Measures

Adversity

1. ***Trauma and Life Events (TALE) Checklist***

   What does it measure: Change in adverse event sequelae
   Description: This 21-item yes/no scale asks participants which of the listed events they have experienced in their lifetime (e.g., sexual abuse, traumatic entry into care). It also asks participants if any of the events they have experienced occurred more than once, and at what age(s) the event(s) occurred. This questionnaire also asks the participant whether those adverse events are affecting them now in any way. Two scores can be formed from this measure: 1) the total number of lifetime adverse events (ranging from 0-20) and 2) how much participants are currently affected by these events (0, "not at all" to 10, "extremely").
   Detailed timeline: Eligibility assessment; 8 weeks post-assessment 6 (follow-up assessment 1)

2. **Trauma Symptom Checklist-40** ***(TSC-40)***

What does it measure: Change in adversity sequelae
Description: The TSC-40 includes 40 items asking about the frequency of mental health symptoms that many people experience after living through one or more adverse events (e.g., crying, feelings of guilt, insomnia). The answers can range from "Never (0)" to "Often (3)." Several studies have examined the validity of this questionnaire among people with psychotic disorders and have found that it is appropriate for use with this population. We will use the total score and the subscale scores (e.g., dissociation, anxiety, depression). Total scores range from 0 to 120; higher scores indicate greater psychopathology.
Detailed timeline: Baseline assessment (study week 1); baseline follow-up appointments (study weeks 2, 2&3; or 2,3, & 4, depending on randomization to intervention start time); pre-intervention assessment 1 (study weeks 3, 4, or 5, depending on randomization to intervention start time; administer immediately prior to intervention session 1); ; intra-intervention assessment 2 (study weeks 6, 7, or 8); administer immediately after intervention session 3) ; intra-intervention assessment 3 (study weeks 9, 10, or 11,; administer immediately after intervention session 6); intra-intervention assessment 4 (study weeks 12, 13, or 14; administer immediately after intervention session 9); intra-intervention assessment 5 (study weeks 15, 16, or 17; administer immediately after intervention session 12); intra-intervention assessment 6 (study weeks 18, 19, or 20; administer immediately after intervention session 15); 8 weeks post-assessment 6 (follow-up appointment 1); 9 weeks post-assessment 6 (follow-up appointment 2)

Functioning

1. Social and Occupational Functioning Assessment Scale *(SOFAS)*

What does it measure: Change in functioning
Description: This clinician-reported instrument measures social and occupational functioning. Ratings range from "1-10 – Persistent inability to maintain minimal personal hygiene/unable to functioning without harming self or others or without considerable external support" to "91-100 – Superior functioning in a wide range of activities." Scores on this measure range from 1 to 100; higher scores indicate greater functioning; lower scores indicate greater impairment in functioning.
Detailed timeline: Baseline follow-up appointments (study weeks 2; 2 and 3; or 2,3, and 4; depending on randomization to intervention start time); pre-intervention assessment 1 (study week 3,4, or 5, depending on randomization); intra-intervention assessment 2 (study week 6,7, or 8, depending on randomization); intra-intervention assessment 3 (study week 9,10, or 11, depending on randomization); intra-intervention assessment 4 (study week 12,13, or 14, depending on randomization); intra-intervention assessment 5 (study week 15,16, or 17, depending on randomization); intra-intervention assessment 6 (study week 18,19, or 20, depending on randomization); 8 weeks post-assessment 6 (follow-up appointment 1); 9 weeks post-assessment 6 (follow-up appointment 2)

2. Clinical Global Impression – Severity of Illness & Improvement of Illness (*CGI-S & -I*)

What does it measure: Change in functioning
Description: The CGI-S measures the clinician's judgement of the severity of the participant's mental illness at this time and the CGI-I measures the degree of improvement from baseline; we will use the total severity score of the CGI-S and the total improvement score of the CGI-I. CGI-I scores range from 1 (Very much improved) to 7 (Very much worse); higher scores indicate worsening, lower scores indicate improvement. CGI-S scores range from 1 (Normal, not ill at all) to 7 (Among the most

extremely ill); higher scores indicate greater illness severity, lower scores indicate low severity. This measure differs from the SOFAS in that it provides a global estimate of illness severity and improvement.
Detailed timeline: Baseline assessment (study week 1), pre-intervention assessment 1 (study week 3,4, or 5, depending on randomization); intra-intervention assessment 6 (study week 18,19, or 20, depending on randomization); 8 weeks post-assessment 6 (follow-up appointment 1)

Psychotic symptoms

1. **Positive and Negative Syndrome Scale *(PANSS - Negative symptoms subscale)***

What does it measure: Change in negative psychotic symptoms
Description: The PANSS, a semi-structured clinical interview, measures positive and negative psychotic symptoms; we will use the total score of the negative symptoms subscale on this measure as an indicator of negative symptoms. Scores range from 7 to 49; higher scores indicate greater negative symptoms.
Detailed timeline: Baseline assessment; pre-intervention assessment 1 (study week 3,4, or 5, depending on randomization); 8 weeks following assessment 6 (follow-up appointment 1)

2. **Positive and Negative Syndrome Scale *(PANSS - Positive symptoms subscale)***

What does it measure: Change in positive psychotic symptoms
Description: The PANSS, a semi-structured clinical interview, measures positive and negative psychotic symptoms; we will use the total score of the positive symptoms subscale on this measure as an indicator of positive symptoms. Scores range from 7 to 49; higher scores indicate greater positive symptoms.
Detailed timeline: Baseline assessment; pre-intervention assessment 1 (study week 3,4, or 5, depending on randomization); 8 weeks following assessment 6 (follow-up appointment 1)

Substance misuse

1. **Alcohol, Smoking, and Substance Involvement Screening Test *(ASSIST)***

What does it measure: Change in substance use
Description: The ASSIST, an 8-item interview, measures substance use. This interview will help establish substance use frequency for both illicit and legal substances. This interview also includes questions asking about the urge to use substances, difficulties in functioning caused by substance use, and difficulties cutting down or stopping substance use. Responses are on a 5-point frequency scale that range from “Never” to “Daily or almost daily.” This measure has been validated for use with individuals with psychosis (Hides et al., 2009; Humeniuk et al., 2008). We will use the total score for each substance as an indicator of substance use. Scores range from 0-39 for each subscale; higher scores indicate substance misuse.
Detailed timeline: Eligibility assessment (week 0); Depending on randomization to intervention start time: administered weeks 3 through 20, 8 weeks following study week 18,19, or 20-, and 9-weeks following study week 18,19, or 20 randomization); 8 weeks post-assessment 6 (follow-up appointment 1); 9 weeks post-assessment 6 (follow-up appointment 2)

Therapeutic alliance

1. **Session Rating Scale - Version 3 *(SRS-3)***

   What does it measure: Change in therapeutic alliance
   Description: The SRS is a 4-item measure of therapeutic alliance. This instrument measures the therapeutic relationship, goals and topics covered in session, therapist approach/method, and the therapy session overall for each therapy session. This information will allow us to assess the impact of therapeutic alliance on symptom change. Participants will fill out this form following each therapy session and will place it in a sealed envelope; therapists will not have access to this information. Total scores range from 0 to 40; higher scores indicate greater therapeutic alliance, and lower scores indicate problems in one or more areas of session therapeutic alliance.
   Detailed timeline: This measure is administered after each intervention session, meaning it is administered through study weeks 4 to 18; 5 to 19; or 6 to 20 (depending on randomization to intervention start time).

Treatment targets

1. **Brief Experiential Avoidance Questionnaire *(BEAQ)***

   What does it measure: Change in avoidance
   Description: This 15-item scale measures experiential avoidance in participants; we will use the overall score on this measure as an indicator of avoidance. Response options range from “Strongly disagree (1)” to “Strongly agree (6).”
   Scores range from 15 to 90; higher scores indicate greater avoidance.
   Detailed timeline: Baseline assessment, assessments 1-6; depending on randomization to intervention start time: administered weeks 3 through 20, 8 weeks following study week 18,19, or 20, and 9 weeks following study week 18,19, or 20 (see description above for more detail)

2. **Beck Hopelessness Scale *(BHS)***

   What does it measure: Change in hopelessness
   Description: This 20-item true/false scale measures state hopelessness in participants; we will use the total score on this measure as an indicator of hopelessness. Scores range from 0 to 20; higher scores indicate greater hopelessness.
   Detailed timeline: Baseline assessment, assessments 1-6; depending on randomization to intervention start time: administered weeks 3 through 20, 8 weeks following study week 18,19, or 20, and 9 weeks following study week 18,19, or 20 (see description above for more detail)

Other targets

1. **Medication tracking**

   What does it measure: Change in medication type and dose
   Description: This author-made measure is meant to assess medication name and dose in order to account for changes in medication when examining changes in symptoms, especially psychotic symptoms, over time.
   Detailed timeline:

Procedure

All new NSEPP patients are currently asked whether they consent to being contacted for research purposes, with approximately 80% agreeing to be contacted. All current patients who consented will be contacted via their preferred method (i.e., email, telephone) and screened with the ASSIST and TALE questionnaires over the phone or in person (see Figure 1 for procedure details). To be eligible for participation, patients must have experienced ≥1 distressing adverse lifetime event listed on the TALE questionnaire that the participant indicates still affects them now, and one score on the ASSIST must be within the "moderate" or "high" risk range for any substance (excluding tobacco products). Additionally, all participants must be aged 19-35 years and diagnosed with a schizophrenia spectrum disorder (e.g., schizophrenia, schizoaffective) within the last 5 years. Lastly, so long as individuals meet the above criteria, and will be enrolled in the NSEPP for the duration of the program, they are eligible for participation in this study. If participants are deemed eligible, a baseline assessment will be scheduled and conducted. This assessment will include three self-report instruments, the BEAQ, BHS, and TSC-40, in addition to several clinician-administered measures (i.e., PANSS, CGI-I & -S, SOFAS) which will be used to respectively assess psychotic symptoms, illness severity, symptom change, and functioning. Demographic information related to participants' age, gender, race, and sexual orientation will also be collected; these variables are critical to collect as participants from a marginalized community (e.g., BIPOC, 2SLGBTQ+) may have different experiences than those who are not a part of a marginalized group.

This assessment will be followed by 1-3 brief follow-up assessments, depending on the randomization to start time (i.e., 2,3, or 4-week delay between initial interview and therapy) to establish a symptom baseline. The participant's treatment start time, decided by randomization, will be communicated to the participant at the baseline interview. However, the fact that the participant will be randomized to a treatment start time will be communicated to the participant as a part of the consent process. The participant will also participate in an assessment prior to beginning the intervention to determine whether symptoms have changed since the initial baseline assessment. The BHS, BEAQ, and TSC-40 will be administered, in addition to the completion of the SOFAS, CGI-I and -S, ASSIST, and PANSS. The intervention, a 15-session course of weekly PE+ therapy, is divided into five sets of three 90-minute sessions: 1) psychoeducation about AEs, SM, and the interplay of both with psychosis; 2) emotion regulation strategies; 3) imaginal exposures, 4) in vivo exposures, and 5) review of treatment and planning for termination and maintenance. After each set of 3 sessions, current symptoms and SM will be assessed using the instruments above (i.e., BEAQ, BHS, TSC-40, ASSIST, PCL-5). After each session, a measure of therapeutic alliance, the Session Rating Scale (SRS; Duncan et al., 2003) will be administered to account for fluctuations in the therapist-participant relationship on assessment scores. Psychotic symptoms will be reassessed using the PANSS after the final session of treatment has been completed. There will also be two follow-up sessions 2-months post-intervention to assess maintenance of therapeutic gains using all the same instruments as the baseline assessment; each session will take approximately 75 minutes. One session will take place exactly 2 months following the final assessment session after session 15 of treatment, and the last assessment session will take place 1 week later. Participants will also be

asked for their feedback on how to further optimize PE+ therapy for use with patients with EPP in the future.

All individuals working on this study will be trained to recognize signs of emotional distress and intervene immediately. The therapist(s) administering psychotherapy in this study will remind participants that they may choose to discontinue their participation at any time. If the participant appears to become very distressed during a psychotherapy session, the therapist will provide calming strategies to the participant; however, if this is ineffective, the researcher may choose to discontinue the participant's session, or reschedule the session. Any event that involves significant participant distress will be reported to the PI (Victoria Patterson) who will then report it to the NSHA Research Ethics Board immediately as an adverse event. If participants report feeling distress, they will be encouraged to speak with their NSEPP clinician and, if necessary, study staff will assist the participant with making an appointment. During the informed consent process, participants will be provided with a consent form that has contact information for agencies (e.g., Mobile Mental Health Crisis Line) who can assist with intense distress in the unlikely event that participants become upset following their participation. This information will be provided to all participants. All adverse events will be reported via an "Adverse Event Notification" form, which will be filled out and submitted to Research Services at Nova Scotia Health as soon as possible following any adverse events.

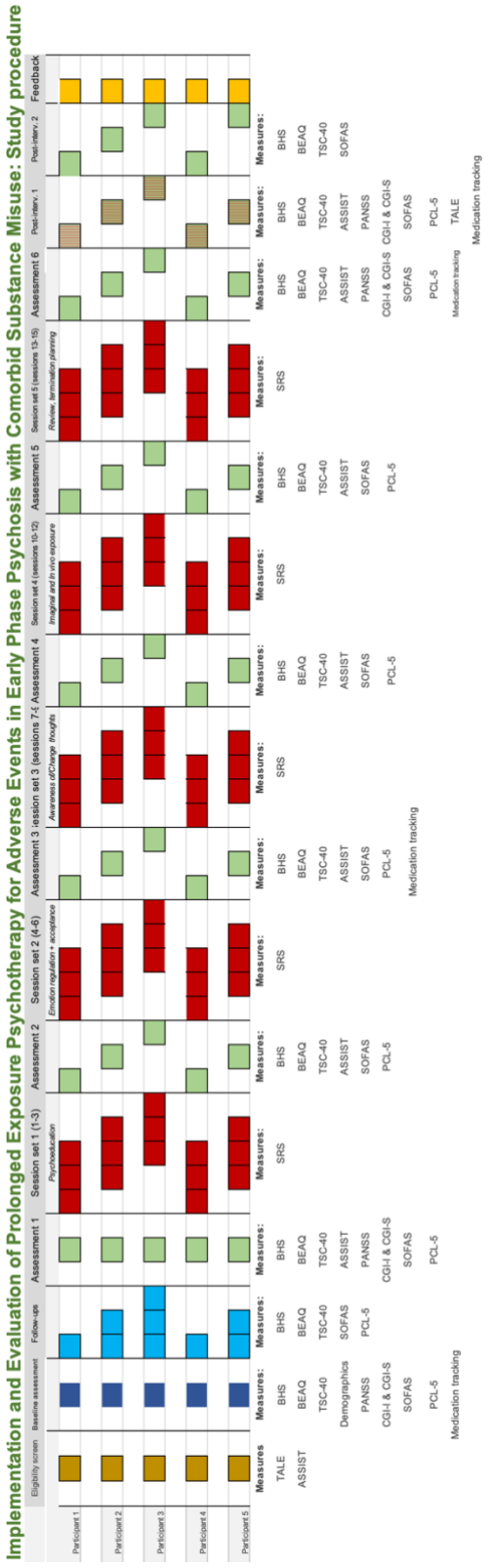

Figure 1. The study's multiple baseline design and procedures

Data analysis plan

The goal of this intervention study is to determine the effect of PE+ therapy on psychotic symptoms, substance misuse, adversity-related sequelae (e.g., PTSD), and functioning. Therefore, the desired outcomes of the analyses will be the significance of symptom change and the maintenance of change over time.

The first hypothesis, that PE+ treatment will result in clinically significant reductions in hopelessness and avoidance, will be addressed using the Reliable Change Index (RCI; Jacobson & Truax, 1991), our chosen analysis, as inferential statistics are not appropriate. A power analysis is not possible to compute given that inferential statistics are not appropriate for RCIs; however 20 participants is typical for studies using the MBD and this number is on par with previously published studies using this design (Frueh et al., 2009). The RCI criteria we will use to determine clinically significant change is that the participants' mean post-intervention assessment scores will be between the scores of a healthy population and a mentally ill population (see Figure 2; change criteria c). This criterion is neither liberal nor conservative and is the most realistic criterion given the multitude of psychological symptoms that we are aiming to treat. We will calculate the numerical criteria needed to assess this change using previously published means and standard deviations of the measures we are using (e.g., PANSS, TSC-40 scores) within studies similar to this one. RCI determines the participant's category of change post-intervention: recovered (i.e., met criteria for clinical change), improved (i.e., have statistically significant change but not large enough to be considered a full recovery), unchanged (i.e., no change over time), and deteriorated (i.e., significant worsening of symptoms over time). The second hypothesis (PE+ treatment will result in clinically significant reductions in negative psychotic symptoms (e.g., anhedonia)), third hypothesis (PE+ treatment will result in clinically significant reductions in the frequency and quantity of substance misuse), and fourth hypothesis (global improvement in functioning from pre- to post-PE+ therapy will occur with gains maintained 2 months-post treatment) will also be addressed using the RCI.

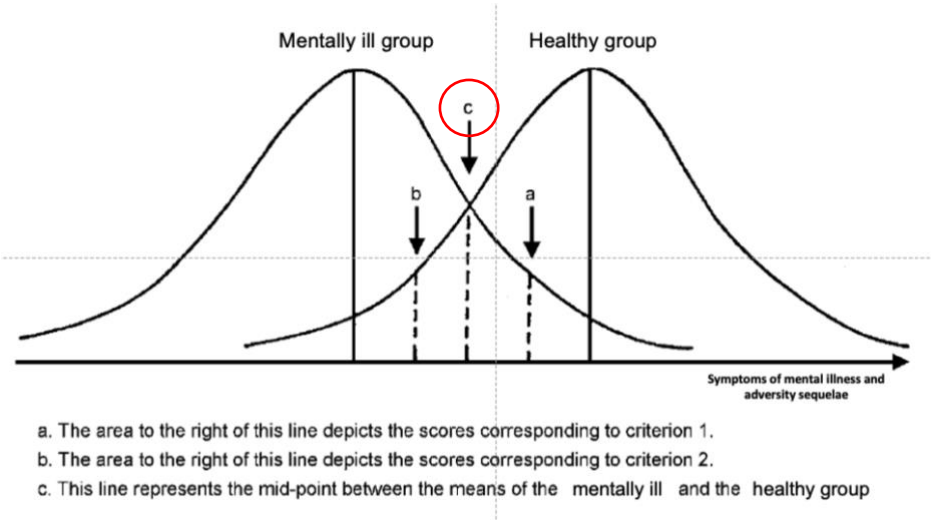

Figure 2. Reliable Change Index (RCI) change criterion

The following table illustrates the scores necessary to obtain to be classified within the four RCI categories:

RCI tables

Core variables

	Adversity TSC-40 total score[1]	Psychotic sx: Positive PANSS[2**]	Psychotic sx: Negative PANSS[2]	Substance use ASSIST[3]	Hopelessness BHS[4]	Avoidance BEAQ[5]
Clinically significant change	Post-treatment Score <18.25 Score decreased from pre-treatment by at least 7.14	Post-treatment score < 8.57 Score decreased from pre-treatment by at least 8.24	Post-treatment score < 9.72 Score decreased from pre-treatment by at least 10.33	Post-treatment score < 18.77 Score decreased from pre-treatment by at least 18.11	Post-treatment score < 4.41 Score decreased from pre-treatment by at least 7.38	Post-treatment score < 49.83 Score decreased from pre-treatment by at least 15.67
Improved	Post-treatment score > 18.25 Score decreased from pre-treatment by at least 7.14	Post-treatment score > 8.57 Score decreased from pre-treatment by at least 8.24	Post-treatment score > 9.72 Score decreased from pre-treatment by at least 10.33	Post-treatment score > 18.77 Score decreased from pre-treatment by at least 18.11	Post-treatment score > 4.41 Score decreased from pre-treatment by at least 7.38	Post-treatment score > 49.83 Score decreased from pre-treatment by at least 15.67
No change	Score decreased from pre-treatment by < 7.14	Score decreased from pre-treatment by < 8.24	Score decreased from pre-treatment by < 10.33	Score decreased from pre-treatment by < 18.11	Score decreased from pre-treatment by < 7.38	Score decreased from pre-treatment by < 15.67
Deteriorated	Score increased from pre-treatment by at least 7.14	Score increased from pre-treatment by at least 8.24	Score increased from pre-treatment by at least 10.33	Score increased from pre-treatment by at least 18.11	Score increased from pre-treatment by at least 7.38	Score increased from pre-treatment by at least 15.67

[1] – Mahato et al., 2017; 30 Indian people aged 18-45 with schizophrenia (clinical group) and 30 Indian people aged 18-45 with no psychiatric history (control group). All completed the TSC-40.

[2] – Baudin et al., 2016, 366 French people aged 15 to 84 with schizophrenia and schizoaffective disorder, 30% of whom have experienced childhood maltreatment and 27% of whom have a cannabis use disorder (clinical group); Frissen et al., 2018, 87 Dutch people aged 16-50 with no first-degree relatives with psychosis (control group). All completed the PANSS.

[3] – Hides et al., 2009; 102 Australian people with first episode psychosis (FEP) with a substance use disorder (clinical group) and 112 Australian people with FEP and no substance use disorder (control group). All participants aged 15-25. All completed the WHO ASSIST.

[4] – Goodby & MacLeod, 2016; 30 patients aged 19-35 with first-episode psychosis (clinical group) and 27 matched community participants aged 19-33 (control group). All completed the Beck Hopelessness Scale (BHS).

[5] – Gámez et al., 2014; 265 American outpatients aged 18-79 with various anxiety disorders and depression (clinical group) and 215 community members aged 24-67 (control group). All completed the BEAQ.

*Scores are for each individual measure score, e.g., a score of 8 on the PANSS is specific to that measure and carries different meaning on the ASSIST
** It is unlikely that participants will have such elevated positive symptoms/elevated positive symptom scores on the PANSS and be able to consent and participate in this study. However, it seems appropriate to use representative scores and form hypotheses in advance, as with any other symptom in this study. Therefore, little to no change, or a lack of clinically significant improvement, during this treatment may not be an indicator of a lack of effectiveness.

Specific adversity-related symptom RCIs:

	TSC-40: Dissociation	**TSC-40: Anxiety**	**TSC-40: Depression**	**TSC-40: Sexual abuse trauma index**	**TSC-40: Sleep disturbance**	**TSC-40: Sexual problems**
Clinically significant change	Post-treatment score < 3.71 Score decreased from pre-treatment by at least 3.06	Post-treatment score < 3.12 Score decreased from pre-treatment by at least 2.57	Post-treatment score < 2.02 Score decreased from pre-treatment by at least 2.83	Post-treatment score < 2.81 Score decreased from pre-treatment by at least 2.33	Post-treatment score < 1.66 Score decreased from pre-treatment by at least 2.42	Post-treatment score < 0.51 Score decreased from pre-treatment by at least 2
Improved	Post-treatment score > 3.71 Score decreased from pre-treatment by at least 3.06	Post-treatment score > 3.12 Score decreased from pre-treatment by at least 2.57	Post-treatment score > 2.02 Score decreased from pre-treatment by at least 2.83	Post-treatment score > 2.81 Score decreased from pre-treatment by at least 0.87	Post-treatment score > 1.66 Score decreased from pre-treatment by at least 2.42	Post-treatment score > 0.51 Score decreased from pre-treatment by at least 2
No change	Score decreased from pre-treatment by < 3.06	Score decreased from pre-treatment by < 2.57	Score decreased from pre-treatment by < 2.83	Score decreased from pre-treatment by < 2.33	Score decreased from pre-treatment by < 2.42	Score decreased from pre-treatment by < 2
Deteriorated	Score increased from pre-treatment by at least 3.06	Score increased from pre-treatment by at least 2.57	Score increased from pre-treatment by at least 2.83	Score increased from pre-treatment by at least 2.33	Score increased from pre-treatment by at least 2.42	Score increased from pre-treatment by at least 2

*All data in this table is based on Mahato et al., 2017. All participants are Indian adults aged 18-45. The clinical group participants (*N* = 30) were diagnosed with schizophrenia while the control group (*N* = 30) had no psychiatric history. All participants completed the TSC-40.

*Scores are for each individual subscale score, e.g., a score of 2 on the TSC-40 dissociation subscale is specific to that subscale and carries different meaning on the TSC-40 sleep disturbance or depression subscale.

Functioning RCIs:

	Functioning: SOFAS[1]	Functioning: CGI-I[2]	Functioning: CGI-S[3]
Clinically significant change	Post-treatment score > 73.31 Score increased from pre-treatment by at least 16.52	Post-treatment score of 1 or 2	Post-treatment score < 3.8 Score decreased from pre-treatment by at least 1.24
Improved	Post-treatment score > 73.31 Score increased from pre-treatment by at least 16.52	Post-treatment score of 3	Post-treatment score > 3.8 Score decreased from pre-treatment by at least 1.24
No change	Score decreased from pre-treatment by < 16.52	Post-treatment score of 4	Score decreased from pre-treatment by < 1.24
Deteriorated	Score decreased from pre-treatment by at least 16.52	Post-treatment score of 5,6, or 7	Score increased from pre-treatment by at least 1.24

[1] – Thompson et al., 2012; 40 Australian people aged 15-25 years old with first-episode psychosis (clinical group) and 30 people aged 15-25 years old with no past or current psychiatric history (control group). All completed the SOFAS.
[2] – Given the structure of the CGI-I, improvement categories are already built into the instrument; therefore, we will use the pre-determined categories to establish significant change. Scoring is as follows: 0 (Not assessed), 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse).
[3]– Segarra et al., 2012; 477 Spanish people aged 18-45 years with first-episode psychosis and a schizophrenia diagnosis (clinical group), and the same 477 people assessed 1 year into treatment (control group)

*Scores are for each individual measure score, e.g., a score of 6 on the SOFAS is specific to that measure and carries different meaning on the CGI-I or -S.

Specific substance use RCIs:

	SU: Alcohol[1]	SU: Cannabis[2]	SU: Amphetamines[3]	SU: Hallucinogens[4]	SU: Opiates[5]
Clinically significant change	Post-treatment score < 4.76 Score decreased from pre-treatment by at least 6.05	Post-treatment score < 4.63 Score decreased from pre-treatment by at least 7.85	Post-treatment score < 2 Score decreased from pre-treatment by at least 7.33	Post-treatment score < 0.22 Score decreased from pre-treatment by at least 0.87	Post-treatment score < 0.42 Score decreased from pre-treatment by at least 8.24
Improved	Post-treatment score > 4.76 Score decreased from pre-	Post-treatment score > 4.63 Score decreased from pre-	Post-treatment score > 2 Score decreased from pre-treatment by at least 7.33	Post-treatment score > 0.22 Score decreased from pre-treatment by at least 0.87	Post-treatment score > 0.42 Score decreased from pre-treatment by at least 8.24

	treatment by at least 6.05	treatment by at least 7.85			
No change	Score decreased from pre-treatment by < 6.05	Score decreased from pre-treatment by < 7.85	Score decreased from pre-treatment by < 7.33	Score decreased from pre-treatment by < 0.87	Score decreased from pre-treatment by < 8.24
Deteriorated	Score increased from pre-treatment by at least 6.05	Score increased from pre-treatment by at least 7.85	Score increased from pre-treatment by at least 7.33	Score increased from pre-treatment by at least 0.87	Score increased from pre-treatment by at least 8.24

*All data is from Hides et al., 2009. All participants are Australian people aged 15-25; the clinical group for each substance below contains individuals with polysubstance use. All participants completed the WHO ASSIST and all substance use disorders were diagnosed using the SCID.

[1] – 45 people with an alcohol use disorder (clinical group) and 169 people without an alcohol use disorder (control group).
[2] – 80 people with a cannabis use disorder (clinical group) and 134 people without a cannabis use disorder (control group).
[3] – 27 people with a stimulant use disorder (clinical group) and 187 people without a stimulant use disorder (control group).
[4] – 16 people with a hallucinogen use disorder (clinical group) and 198 people without a hallucinogen use disorder (control group).
[5] – 8 people with an opiate use disorder (clinical group) and 206 people without an opiate use disorder (control group).

*Scores are for each individual subscale score, e.g., a score of 4 on the alcohol subscale of the ASSIST is specific to that subscale and carries different meaning on the cannabis or opiates subscale.

References

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